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Lijfering, Willem M.; Tichelaar, Ynse I. G. V.

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COMMENTARY

Direct oral anticoagulant use and risk of perioperative bleeding: Evidence of absence or absence of evidence?

Willem M. Lijfering MD, PhD¹ | Ynse I. G. V. Tichelaar MD, PhD^{2,3}¹Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands²Department Internal Medicine, Division Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands³Department of Hematology, Division of Hemostasis and Thrombosis, University Medical Center Groningen, University of Groningen, Groningen, the NetherlandsThis is a commentary on Shaw *et al* [2018, in this issue]: <https://doi.org/10.1002/rth2.12076>**Correspondence**

Willem M. Lijfering, Department of Clinical Epidemiology C7-P, RC Leiden, the Netherlands.

Email: w.m.lijfering@lumc.nl**KEYWORDS:**

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For patients who are receiving treatment with oral anticoagulants and require an elective operation or other invasive procedure, interrupting anticoagulation is often required. Each year, this common clinical scenario affects approximately one in six patients on oral anticoagulation.^{1,2} The perioperative management of such patients is pertinent to many clinicians, including internists, surgeons, anesthesiologists, family physicians, and dentists.^{2,3}

In this issue of *RPTH*, Shaw and colleagues provide data on the safety of perioperative interruption of direct oral anticoagulants (DOACs) for elective invasive procedures in patients with atrial fibrillation.⁴ The clinical scope of this problem is important. Not only are DOACs fast replacing vitamin K antagonists (VKAs) as anticoagulant treatment for stroke prevention in patients with atrial fibrillation,⁵ but as a previous survey among medical practitioners showed, the effects of DOACs at time of invasive procedures are often unrecognized.⁶ Previous expert narrative reviews have provided guidance to clinicians on the management of DOACs in the perioperative period,⁴ and in order to update these expert reviews with clinical data, Shaw *et al.* conducted a systematic review and meta-analysis of the literature involving four cohort studies and four clinical trials. They investigated in a total of 14 446 patients (who used a DOAC or VKA) the 30-day risk of thromboembolic events, bleeding, and death. Unfortunately, of the eight studies included, three did not describe their perioperative anticoagulation protocols for DOACs, but the other five studies more or less did. For dabigatran

these perioperative protocols were reasonably well described and they were based on the creatinine clearance, the corresponding estimated half-life of dabigatran (13-27 hour depending on renal function),^{7,8} and on whether the invasive procedure was deemed as having a low or high risk of bleeding.^{1,9,10} For rivaroxaban, those who temporarily interrupted anticoagulant treatment for ≥ 3 days due to any cause were considered to have interrupted their treatment due to an invasive procedure.¹¹ For apixaban, each procedure was classified as either "no interruption" (if the study drug was not interrupted or interrupted on the same day of the procedure) or "any interruption" (if the study drug was stopped between one and seven days before the procedure), but the final decision about when apixaban would be interrupted was left to local investigators.¹² Therefore, we do not exactly know the perioperative management in the included apixaban and rivaroxaban studies.^{11,12} Also, none of these five studies took into account the thromboembolic risk of the patients during the perioperative phase, as is advised by the American College of Chest Physicians and other expert opinion panels.^{3,4} Furthermore, from the apixaban study it was unclear if for procedures with minimal bleeding risk, like dental or ocular procedures, apixaban was interrupted or not,¹³ while for the rivaroxaban and dabigatran studies in at least some of these situations anticoagulation therapy was interrupted.⁹⁻¹² This is important to note because expert opinion panels advise not to interrupt anticoagulation in minimal bleeding risk procedures.^{2,3} Nevertheless, Shaw *et al.* had to make do with

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what information they had and with it they found that the 30-day risk for thromboembolic and major bleeding events was 0.4% and 1.8%, respectively. Based on these absolute risks the authors rightly conclude that these findings seem reassuring. However, despite the large number of patients involved and the meticulous systematic review and meta-analysis that the authors performed, this study should not be seen as an endpoint but as a starting point, which is also urged by the authors at the end of their discussion.⁴ Below, we discuss some issues that should prompt more clinically oriented research in this field with predefined endpoints, and propose a protocol for DOAC interruption that seems reasonable with the evidence that is presently known (Table 1).

1 | GENERALIZABILITY

Of the eight studies that were meta-analyzed, four involved patients who were included in randomized clinical trials ($n = 9939$).⁴ Previous studies have shown that VKAs are often prescribed to patients who would not have qualified for clinical trials,¹³ which is likely to be the same for patients who are prescribed a DOAC.¹⁴ Randomized trials prioritize internal over external validity, and researchers therefore strive to include patients who, for instance, are more likely to adhere to the prescribed procedures, are not likely to undergo major surgery, have a life-expectancy longer than the trial duration, and are capable of giving informed consent. This is a reasonable approach that is needed before one can even start thinking about the more heterogeneous real world.¹⁴ In the meta-analysis, Shaw et al. did include patients with atrial fibrillation on DOAC who had an invasive procedure *outside* clinical trial settings, but these

comprised only 7% ($n = 679$) of the total study population (ie, all other patients came from clinical trials). Therefore, it can be questioned whether the relatively low outcome rates of thromboembolic and major bleeding events at 30-days post invasive procedure are due to a safe interruption strategy only. Large observational studies that include consecutive patients with atrial fibrillation on DOAC and who require an elective invasive procedure are needed to address this issue.

2 | HIGH BLEEDING RISK INVASIVE PROCEDURES

Of the eight studies included, there were three that exclusively concerned patients undergoing permanent pacemaker insertion or implantable cardioverter defibrillator procedures. These invasive procedures are considered to have a minimal bleeding risk and in which anticoagulation can be continued during the procedure.^{2,3} It is therefore not surprising that in these studies none of the patients developed a thromboembolic event or (when reported) a major bleeding. But also in the other five studies that included patients undergoing a variety of procedures, the large majority of patients underwent procedures that are considered to be minimal/low bleeding risk procedures. The clinically relevant procedures where the major bleeding risk is high (ie, $\geq 2\%$ within two days post-surgery), like surgery with extensive tissue injury, cancer surgery, joint arthroplasty, or reconstructive plastic surgery,^{2,3} are under-represented in the meta-analysis. It is unfortunate that the authors did not have access to individual patient data as this might have answered the question what the postoperative bleeding- and

TABLE 1 Proposed protocol for DOAC interruption at time of an invasive procedure^a

DOAC type	Estimated half-life, h	Bleeding risk of the procedure	Interruption timing of DOAC							
			Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3
Dabigatran (eGFR ≥ 50 ml/min)	≈ 13 -15 h	High			stop	stop	stop	stop	stop ^c	restart
		Low				stop	stop	restart		
		Minimal					continue ^b			
Dabigatran (eGFR < 50 ml/min)	≈ 18 -27 h	High	stop	stop	stop	stop	stop	stop	stop ^c	restart
		Low		stop	stop	stop	stop	restart		
		Minimal					continue ^b			
Rivaroxaban	≈ 5 -9 h	High			stop	stop	stop	stop	stop ^c	restart
		Low				stop	stop	restart		
		Minimal					continue ^b			
Apixaban	≈ 12 -17 h	High			stop	stop	stop	stop	stop ^c	restart
		Low				stop	stop	restart		
		Minimal					continue ^b			

DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate.

Definitions of which procedures are associated with minimal, low and high bleeding risks can be found in Ref. 4.

^aAdapted from the PAUSE protocol,¹⁷ with some modifications (i.e., addition of minimal bleeding risk category).

^bMay consider interrupting DOAC therapy on the day of the procedure.

^cMay consider to restart DOAC therapy two days after the procedure.

thromboembolic risk is in patients who underwent an elective high bleeding risk invasive procedure. Future studies should include larger numbers of patients who undergo such high bleeding risk procedures.

3 | TO MEASURE OR NOT TO MEASURE

As acknowledged by the authors, the results they found need validation in large prospective management studies where pre-operative DOAC levels are also measured. Although not reported for apixaban and rivaroxaban, dabigatran levels are related with bleeding.¹⁵ There is a paucity of studies that actually looked at direct oral anticoagulation levels at time of an invasive procedure; to our knowledge there is currently only one study available that addressed this issue.¹⁶ In this cohort study (which was a sub-analysis from one of the cohort studies that was reported in the meta-analysis⁹), performed by Douketis and colleagues, it was shown that in 181 patients who took dabigatran and were requesting an elective invasive procedure, the anticoagulant effect had not worn off in all patients despite that they withheld dabigatran therapy for 24-48 hours before the procedure. Approximately 15% had residual dabigatran levels at time of the procedure.¹⁶ As acknowledged by the authors, their study was unable to show that their strategy was necessarily safe, even though only one major bleed occurred in a patient in whom no anticoagulant effect was observed. Probably this issue is best explained by a number needed to harm (NNH), which calculates the number of patients that should be treated with dabigatran to produce one major bleed, opposed to patients who were unexposed to therapeutic dabigatran levels at the time of the procedure. We calculated that even for a NNH of 20 one would need a study of approximately 500 patients. The fact that the aforementioned study was underpowered to find even a NNH of 20 is important, as it bears forward the need for a larger study where preoperative DOAC levels are measured.

4 | STANDARD OF CARE APPROACH, EVIDENCE-BASED

Recently, the design and rationale of the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study for patients on a DOAC who need elective surgery or an invasive procedure has been published.¹⁷ PAUSE will study in an observational design with longitudinal follow-up if a standardized, patient-specific perioperative management tool for patients on DOACs with atrial fibrillation works in terms of safety and efficacy, and has a secondary aim to determine the effect of residual anticoagulation at time of the procedure. Initiatives like PAUSE are urgently needed.

In conclusion, the current study of Shaw et al. adds some scientific support for safe interruption of anticoagulation in patients who are treated with DOACs and require elective surgery or an invasive

procedure. Nevertheless, what the best perioperative management is in such patients is still uncertain.

RELATIONSHIP DISCLOSURE

The authors state that they have no conflict of interest.

AUTHOR CONTRIBUTION

WML and YIGVT were the main investigators of the manuscript. WML wrote the first draft of the manuscript and the final version. YIGVT was responsible for review of the manuscript.

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